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Quantification of Collateral Flow in Humans: A Comparison of Angiographic, Electrocardiographic and Hemodynamic Variables

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OBJECTIVES Evaluation of collateral vascular circulation according to hemodynamic variables and its relation to myocardial ischemia.

BACKGROUND There is limited information regarding the hemodynamic quantification of recruitable collateral vessels.

METHODS Angiography of the donor coronary artery was performed before and during balloon coronary occlusion in 63 patients with one vessel disease. Patients were divided into groups of those with an absence of collateral vessels (group 1, n = 10), those with recruitable collateral vessels (group 2, n = 23) and those with spontaneously visible collateral vessels (group 3, n = 30). During balloon inflation the coronary wedge/aortic pressure ratio (Pw/Pao) was determined as were collateral blood flow velocity variables, using a 0.014″ Doppler guide wire. Myocardial ischemia was defined as ≥0.1 mV ST-shift on a 12 lead electrocardiogram at 1 min coronary occlusion.

RESULTS Myocardial ischemia was present in all patients of group 1, in 14 patients of group 2 and in 3 patients of group 3. Recruitable collateral flow without ischemia showed similar hemodynamic values as in group 3 while these values were similar to group 1 in regard to the presence of recruitable collateral vessels showing ischemia. Logistic regression analysis revealed both Pw/Pao and Vi_{col} as independent predictors for the function of collateral vessels.

CONCLUSIONS Hemodynamic variables of collateral vascular circulation are better markers of the functional significance of collateral vessels than is coronary angiography. The total collateral blood flow velocity integral and coronary wedge/aortic pressure ratio are good and independent predictors of the function of collateral vessels producing complementary information. (J Am Coll Cardiol 1999;33:670–7) © 1999 by the American College of Cardiology

Numerous reports have underlined the functional significance of the coronary collateral circulation in obstructive coronary artery disease (1–8). Several studies have reported the evaluation of the coronary collateral circulation using hemodynamic variables (pressure or blood flow velocity) (9–19). However, only a limited number of studies have been performed using both pressure and flow-derived variables which are of crucial importance for the evaluation of the collateral vascular circulation (20,21). Coronary balloon occlusion is a suitable model to study the hemodynamics of collateral vessels in humans in relation to its protective function.

Initial reports evaluated hemodynamic estimates of the collateral vascular circulation in relation to the angiographic grading of collateral vessels according to Rentrop's classification before balloon coronary occlusion. However, several studies emphasized the relevance of angiography during balloon coronary occlusion using an additional arterial catheter for documentation of recruitable collateral vessels (10,17,20). Consequently, the purpose of this study was to evaluate the relationship between angiographic presence of collateral vessels, including recruitability of collaterals, during coronary occlusion and hemodynamic variables of the collateral vascular circulation. The variables were related to the function of collateral vessels determined by signs of ischemia during brief coronary occlusion. Furthermore, these findings were compared to the variables obtained in patients with spontaneously visible collateral vessels in subtotal or total coronary occlusions.

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METHODS

Sixty-three patients (mean age 55 ± 10, range 33–75 years) with one-vessel coronary artery disease, referred to our

Abbreviations and Acronyms

Rcoll	= collateral vascular resistance
Pw	= coronary occlusion wedge pressure
Pw/Pao	= coronary wedge/aortic pressure ratio
dVi_{col}	= diastolic collateral blood flow velocity integral
Rrec	= peripheral vascular resistance of the recipient coronary artery
ROC	= receiver operating characteristics
sVi_{col}	= systolic collateral blood flow velocity integral
Vi_{col}	= total collateral blood flow velocity integral

institution for PTCA, were studied prospectively. Inclusion criteria were: 1) angina pectoris refractory to medical therapy, and 2) coronary narrowing or total coronary occlusion suitable for balloon angioplasty. Exclusion criteria were: 1) multilesion one-vessel disease, 2) previous cardiac surgery, 3) peripheral artery disease limiting arterial access. A total of 27 (43%) of the 63 patients underwent cardiac catheterization due to postinfarct angina, 6 patients experienced a Q-wave infarction. Informed consent was given in accordance with the rules of the Institutional Ethics Committee which approved the study.

Cardiac catheterization. All antianginal medications and aspirin (100 mg) were continued until cardiac catheterization. Lorazepam (1 mg) was administered orally before the procedure. Nitroglycerin (0.1 mg i.c.) was administered before quantitative coronary angiography and repeated only in case of the occurrence of coronary spasm. Cardiac catheterization was performed using the percutaneous femoral approach. A 6 or 7 Fr sheath was inserted into both the right and left femoral arteries. One guiding catheter was used for introduction of a Doppler guide wire and the balloon catheter in the recipient coronary artery and one additional guiding catheter was used for angiography of the donor coronary artery. At the beginning of the catheterization, all patients received heparin intravenously (5000 U) as a bolus. Additional heparin was administered if the procedure lasted more than 90 minutes.

The angiographical grading of collateral vessels was determined before and during the first balloon inflation. During the subsequent balloon inflations, collateral flow velocity was obtained. Subsequently, the Flowire was removed and coronary wedge pressure was measured through a fluid-filled lumen during at least two additional balloon inflations.

Quantitative coronary angiography. Angiography of the donor artery was performed before angioplasty by automatic contrast injection (Angiomat 3000, Liebel-Flarsheim Co., Cincinnati, Ohio; right coronary artery 4 to 6 ml, 7 ml/s; left coronary artery 6 to 8 ml, 9 ml/s). Cineangiography was continued until there was no further opacification of the injected vascular bed. A repeat arteriogram of the donor artery was obtained at 30 seconds during the first balloon inflation. The severity of the coronary narrowing was determined by an automated contour detection algorithm (ARTREK, ADAC Laboratories, Evendale, California) in two orthogonal projections, using the guiding catheter as a reference, to obtain the percentage diameter stenosis and the minimal lumen diameter.

Collateral vessels were graded according to Rentrop's classification (22); 0 = no filling of collateral vessels; 1 = filling of collateral vessels without any epicardial filling of the artery to be dilated; 2 = partial epicardial filling by collateral vessels of the artery to be dilated; and 3 = complete epicardial filling by collateral vessels of the artery to be dilated. The grading of the collateral vessels was performed independently by 2 angiographers and a consensus was reached in the case of disagreement ($\kappa = 0.85$, CI 0.77–0.93). Collateral vessels were considered recruitable when they were absent before coronary occlusion (grade 0 or 1) and present during coronary occlusion (grade 2 or 3, $\kappa = 0.94$, CI 0.88–1.00). Collateral vessels were classified spontaneously visible when they were grade 2 or 3 before coronary occlusion. Electrocardiographic signs of ischemia during coronary occlusion of one minute duration were evaluated by the maximal ST-segment changes in a 12-lead electrocardiogram. Ischemia was defined as $\geq$1 mV ST-segment shift in at least one lead. Heart rate obtained from the electrocardiogram was monitored throughout the procedure.

Collateral flow velocity. A 0.014″ Doppler guide wire, equipped with a forward-directed piezoelectric Doppler crystal at its tip (FloWire, EndoSonics, Rancho Cordova, California) was inserted in the recipient coronary artery in order to accurately assess collateral blood flow velocity distal to the balloon occlusion (23). The Doppler signals of the FloWire were generated by 12-MHz pulsed Doppler velocimeter and were processed by a real-time spectral analyzer using fast Fourier transformation (FloMap, EndoSonics, Rancho Cordova, California). Coronary blood flow velocity in the recipient artery was assessed during the first and subsequent balloon inflations of approximately one minute duration. Collateral flow was considered present in the case of a blood flow velocity signal with a diastolic maximal peak velocity exceeding 5 cm/s. Collateral flow in the recipient coronary artery during balloon inflation was determined by the total (Vi_{col}), systolic (sVi_{col}) and diastolic collateral blood flow velocity integral (dVi_{col}) and the diastolic maximal peak velocity ($dMPV_{col}$). In biphasic collateral blood flow velocity signals, Vi_{col} was calculated as the sum of the absolute values of sVi_{col} and dVi_{col}. These collateral blood flow velocity variables were assessed off-line by manual tracing of the peak blood flow velocity pattern from a digitized video-frame, averaged over three consecutive beats, using a software program available on the Internet (NIH Images 1.58, National Institutes of Health, Bethesda, Maryland).

Pressure measurements and collateral resistance. Mean aortic pressure (Pao) was measured at the tip of the guiding catheter. The mean coronary occlusion wedge pressure (Pw) was measured at the tip of the balloon catheter through the fluid-filled lumen during balloon inflation. Both measurements were assessed simultaneously during balloon coronary occlusion to determine the Pw/Pao ratio. The collateral vascular resistance (Rcoll) was assessed by relating Vi_{col} to the pressure gradient (Pao − Pw) upon the collateral vascular bed using the assumption that the resistance of the epicardial donor coronary artery is negligible: Rcoll (mm Hg/cm) = (Pao − Pw)/Vi_{col}. The myocardial vascular resistance of the recipient coronary artery (Rrec) was calculated as: Rrec = Pw/Vi_{col} (21).

Statistics. Continuous variables are expressed as means ± 1 SD. The two sample *t* test was used to compare continuous variables of patients with and without signs of myocardial ischemia. Continuous data without a normal distribution or without similar variances were compared using the Mann-Whitney *U* test. Analysis of variance (ANOVA) for ordered groups (considering a significant linear trend) was used to compare continuous data between the ordered patient groups classified as having no collateral vessels, those with recruitable collateral vessels and those with spontaneously visible collateral vessels. Frequency data are presented together with summaries as rounded percentages. The Chi-squared test was used for comparing two proportions and the Chi-squared test for trend was used to compare frequency data of the ordered patient groups. The predictive values of the pressure and collateral blood flow velocity variables in relation to ECG signs of ischemia were evaluated using their respective areas under the receiver operating characteristics (ROC) curves. The best cut-off value for each variable of interest was determined by the value representing the largest area (sensitivity × specificity) of the specific ROC curve. Logistic stepwise regression analysis was performed to determine independent explanatory variables of functional recruitable collateral vessels. For this reason, continuous pressure and collateral blood flow velocity variables were transformed into binominal values according their best cut-off value. A p value <0.05 was considered statistically significant.

RESULTS

Angiographic and functional classification of collateral vessels. Angiographic opacification of the collateral vessels before balloon angioplasty was graded 0 in 23 patients, graded 1 in 10 patients, graded 2 in 13 patients and graded 3 in 17 patients. During balloon coronary occlusion, 2 patients were graded 0, 8 patients were graded 1, 25 patients were graded 2 and 28 patients were graded 3, resulting in: 10 patients with an absence of collateral vessels (Group 1), 23 patients with recruitable collateral vessels (Group 2) and 30 patients with spontaneously visible collateral vessels (Group 3). Baseline characteristics of these 3 groups are listed in Table 1.

Electrocardiographic signs of ischemia during balloon coronary occlusion were present in 26 of the 63 patients. Ischemia was present in all the patients without collateral vessels, in 14 of the 23 patients (61%) with recruitable collateral vessels and in only 3 of the 30 patients (10%) with spontaneously visible collateral vessels.

Hemodynamic variables of the collateral vascular circulation in relation to myocardial ischemia. Pressure measurements were successful in all patients. Of all the collateral blood flow velocity and pressure variables, only Vi_{col}, dVi_{col}, Pw and Pw/Pao revealed higher values in patients with spontaneously visible collateral vessels and lower values in patients without collateral vessels during balloon coronary occlusion as compared to the values measured in recruitable collateral vessels (Table 2). Of these variables, only Vi_{col}, Pw and Pw/Pao were useful in differentiating between functional and nonfunctional recruitable collateral vessels (Table 2). The values of Vi_{col}, Pw and Pw/Pao measured in nonfunctional recruitable collateral vessels were similar to the values measured in patients without collateral vessels during balloon occlusion while values measured in functional recruitable collateral vessels were equal to values measured in spontaneously visible collateral vessels (Table 2).

Direct comparison of blood flow velocity and pressure measurements in predicting the functionality of collateral vessels. The ROC curves of the collateral blood flow velocity variables (Vi_{col}, dVi_{col}, sVi_{col} and $dMPV_{col}$) and the pressure variables (Pw and Pw/Pao) for the presence of ischemia are depicted in Figure 1. The Vi_{col} generated the largest area under the ROC curve (Table 3). However, the area under the curve of Vi_{col} was not significantly different from the areas under the ROC curves of dVi_{col} and Pw/Pao and Pw. The area under the ROC curve of sVi_{col} was significantly smaller as compared with the other variables (Table 3).

Although there was no relevant difference between the areas under the curves of Vi_{col} and Pw/Pao (Table 3), their relationship was modest ($r = 0.61$, $p < 0.0001$, Fig. 2). Logistic regression analysis for the presence of ischemia during balloon occlusion was performed to test whether these two variables were independent. To this end, all blood flow velocity and pressure variables were transformed into binominal variables using their best cut-off values (Table 3). The Vi_{col} and Pw/Pao were the only independent predictors of ischemia after stepwise logistic regression analysis. The regression equation for the model using these variables is: logit (p) = −2.21 + 2.89 (Pw/Pao ≤0.30) + 2.54 (Vi_{col} ≤6.0), $p < 0.0001$. The overall accuracy of this regression equation was 0.84 (Fig 2).

Table 1. Baseline and Angiographic Characteristics of Patients Without Collateral Vessels (Group 1), Recruitable Collateral Vessels (Group 2) and Spontaneously Visible Collateral Vessels (Group 3)

Characteristic	Group 1 n = 10	Group 2 n = 23	Group 3 n = 30	p-value
Age (yr)	59 ± 11	53 ± 9	56 ± 10	0.27
Male	6 (60%)	19 (83%)	19 (63%)	0.24
AP (NYHA):				
2	2 (20%)	2 (9%)	5 (17%)	0.54
3	5 (50%)	13 (57%)	21 (70%)	
4	3 (30%)	7 (30%)	3 (10%)	
Duration of AP (mos)	4.8 ± 3.2	6.9 ± 9.8	7.4 ± 7.9	0.47
Smoking	5 (50%)	10 (43%)	14 (47%)	0.94
Hypertension	2 (20%)	6 (26%)	9 (30%)	0.82
Hypercholesterolemia	5 (50%)	17 (74%)	20 (67%)	0.41
Diabetes mellitus	0 (0%)	1 (4%)	2 (7%)	0.69
Previous myocardial infarction	1 (10%)	7 (30%)	19 (63%)	0.004
Medication:				
Nitrates	5 (50%)	13 (57%)	23 (77%)	0.17
Beta-blocker	8 (80%)	23 (100%)	25 (83%)	0.10
Calcium-antagonist	8 (80%)	18 (78%)	24 (80%)	0.99
Treated coronary artery:				
LAD	9 (90%)	17 (74%)	17 (57%)	0.17
LCx	0 (0%)	2 (9%)	1 (3%)	
RCA	1 (10%)	4 (17%)	12 (40%)	
Proximal lesion location	4 (40%)	6 (26%)	14 (47%)	0.31
TIMI flow:				
0	0 (0%)	0 (0%)	17 (57%)	< 0.0001
1	0 (0%)	0 (0%)	10 (33%)	
2	0 (0%)	5 (22%)	2 (7%)	
3	10 (100%)	18 (78%)	1 (3%)	
% Diameter stenosis	70 ± 7	81 ± 10	96 ± 11	< 0.0001

AP = angina pectoris; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; NYHA = New York Heart Association; RCA = right coronary artery; TIMI = thrombolysis in myocardial infarction.

DISCUSSION

This is the first study evaluating the functional significance of coronary collateral vessels in relation to pressure and flow-derived variables in a relatively large cohort of patients. The results show a gradual increase in hemodynamic estimates of the collateral vascular circulation in patients without collateral vessels to patients with maximal development of collateral vessels in subtotal or total coronary occlusions. The assessed hemodynamic variables are better markers for the evaluation of functional significance of recruitable collateral vessels than is coronary angiography. Furthermore, Vi_{col} and Pw/Pao are independent predictors for development of myocardial ischemia during brief coronary occlusion emphasizing that the assessment of both variables provides complementary information.

Coronary angiography and hemodynamic variables for evaluation of the collateral vascular circulation in humans. *Previous clinical studies.* Many clinical investigations have demonstrated a positive relationship between the angiographic classification of collateral vessels assessed before balloon occlusion and the occurrence of ischemia or ventricular wall motion disturbances during subsequent coronary balloon occlusions (10,13,14). However, the majority of these studies did not include an assessment of recruitable collateral vessels. Subsequent reports demonstrated that the grading of collateral vessels during balloon angioplasty was significantly correlated with ST-segment shifts and the extent of wall motion disturbances during brief coronary occlusion, emphasizing the relevance of documentation of recruitable collateral vessels (10,15). Recruitability of collateral vessels was associated with hemodynamic estimates of the collateral vascular circulation yielding a higher value of Pw (12), Pw/Pao (20) or collateral blood flow velocity measured in the ipsilateral (20) and/or contralateral coronary artery (17,20) as compared with those patients without collateral vessels during balloon occlusion. However, preliminary findings by Meier et al. (12) demonstrated that not all patients with recruitable collateral vessels were protected from ischemia during brief balloon occlusion, suggesting that coronary angiography may be inadequate to assess the functional significance of recruitable collateral vessels. A direct comparison between the angiographic and the hemodynamic variables of recruitable collateral vessels in the development of myocardial ischemia during balloon occlusion was not performed in these studies.

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Table 2. Hemodynamic Values Measured in the Patient Group Without Collateral Vessels (Group 1), Recruitable Collateral Vessels (Group 2) and Spontaneously Visible Collateral Vessels (Group 3) in Patients With and Without Ischemia During Balloon Angioplasty

	Group 1		Group 2			Group 3		
	Ischemia (n = 10)	No Ischemia (n = 0)	Ischemia (n = 14)	No Ischemia (n = 9)	All (n = 23)	Ischemia (n = 3)	No Ischemia (n = 27)	All (n = 30)
Heart rate (beats/min)	65 ± 15	—	68 ± 10	64 ± 11	66 ± 10	91 ± 12†	64 ± 10*	66 ± 13
Pao (mm Hg)	96 ± 13	—	97 ± 11	88 ± 10	93 ± 11	99 ± 3	100 ± 12†	100 ± 11
Pw (mm Hg)	22 ± 8	—	27 ± 8	36 ± 11*	30 ± 10	47 ± 82†	45 ± 13	45 ± 13†
Pw/Pao	0.24 ± 0.08	—	0.28 ± 0.08	0.41 ± 0.13*	0.33 ± 0.12	0.47 ± 0.09†	0.45 ± 0.11	0.45 ± 0.11†
$dMPV_{col}$ (cm/s)	3.6 ± 4.8	—	10.1 ± 9.2†	15.6 ± 9.4	12.3 ± 9.5	16.0 ± 8.2†	17.4 ± 9.1	17.3 ± 8.9†
dVi_{col} (cm)	0.6 ± 0.8	—	2.2 ± 2.3†	3.9 ± 2.9	2.9 ± 2.7	4.1 ± 4†	7.0 ± 4.0†	6.7 ± 4.0†
sVi_{col} (cm)	1.9 ± 2.2	—	2.2 ± 2.1	6.7 ± 3.8*	3.9 ± 3.6	2.5 ± 0.5	3.1 ± 1.9†	3.1 ± 1.8
Vi_{col} (cm)	2.5 ± 2.0	—	4.4 ± 3.2	10.6 ± 5.2*	6.8 ± 5.0	6.7 ± 3.9	10.2 ± 4.9	9.8 ± 4.9†
Rcoll (mm Hg/cm)	44.0 ± 34.9	—	33.4 ± 36.7	5.8 ± 2.7*	22.6 ± 31.4	10.6 ± 7.6	6.5 ± 3.1	6.9 ± 3.8†
Rrec (mm Hg/cm)	9.5 ± 5.3	—	5.7 ± 2.7	3.7 ± 1.3	4.8 ± 5.7	8.2 ± 3.2	5.2 ± 2.6	5.5 ± 7.5†

* $p < 0.05$, compared to patients with ischemia in the same group; † $p < 0.05$; ANOVA for ordered patient groups. $dMPV_{col}$ = diastolic collateral maximal peak velocity; dVi_{col} = diastolic collateral blood flow velocity integral; Pao = mean aortic pressure; Pw = mean coronary wedge pressure; Rcoll = collateral resistance, Rrec = peripheral resistance of the recipient coronary artery; sVi_{col} = systolic collateral blood flow velocity integral; Vi_{col} = total collateral blood flow velocity integral.

Results of the present study. The present study shows that the number of patients developing signs of myocardial ischemia during brief coronary occlusion is reduced in those patients with recruitable or spontaneously visible collateral vessels which is in accordance with the aforementioned clinical studies. However, a variable protective effect was noted in patients with recruitable collateral vessels which is in keeping with the observations by Meier et al. (12). Patients with and without electrocardiographic signs of myocardial ischemia could be differentiated according to the hemodynamic variables of the collateral vascular circulation (Pw, Pw/Pao and Vi_{col}) indicating that these variables are better markers of the protective effect of recruitable collateral vessels. Moreover, the hemodynamic variables measured in patients with recruitable collateral vessels showing absence of myocardial ischemia were similar to the values obtained in patients with spontaneously visible collateral vessels while these variables measured in patients with recruitable collateral vessels with ischemia were similar to the values obtained in patients without collateral vessels during balloon angioplasty. This indicates that the gradual increase in the mean value of Pw/Pao and Vi_{col} from patients without collateral vessels to patients with spontaneously visible collateral vessels is in fact a rather abrupt transition with respect to the functional significance of collateral vessels. These findings emphasize the limitations of angiographical grading of collateral vessels to evaluate the protective effect of recruitable collateral vessels in an individual patient and underscores the value of hemodynamic variables of the collateral vascular circulation.

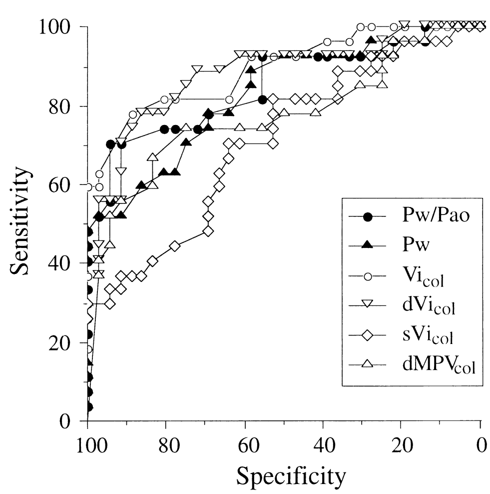

Figure 1. Receiver operating characteristic curves for the presence of ischemia of the hemodynamic variables measured. $dMPV_{col}$ = diastolic collateral maximal peak velocity; dVi_{col} = diastolic collateral blood flow velocity integral; Pw = mean coronary wedge pressure; Pw/Pao = coronary wedge/aortic pressure ratio; Rcoll = collateral resistance; Rrec = peripheral resistance of the recipient coronary artery; sVi_{col} = systolic collateral blood flow velocity integral; Vi_{col} = total collateral blood flow velocity integral.

Table 3. Receiver Operating Characteristic Curves of Angiographical and Hemodynamic Variables in Relation to the Absence and Presence of Ischemia

	AUC	BCV	Sensitivity (%)	Specificity (%)
Vi_{col} (cm)	0.89 ± 0.04	6.0	78	89
dVi_{col} (cm)	0.87 ± 0.05	2.8	78	86
Pw/Pao	0.85 ± 0.05	0.30	70	94
Pw (mm Hg)	0.82 ± 0.05	35	78	69
$dMPV_{col}$ (cm/s)	0.77 ± 0.06	10	67	83
sVi_{col} (cm)	0.71 ± 0.07*	2.5	70	64

* $p < 0.05$ as compared with all other variables. AUC = area under the curve; BCV = best cut-off value; other abbreviations as in Table 2.

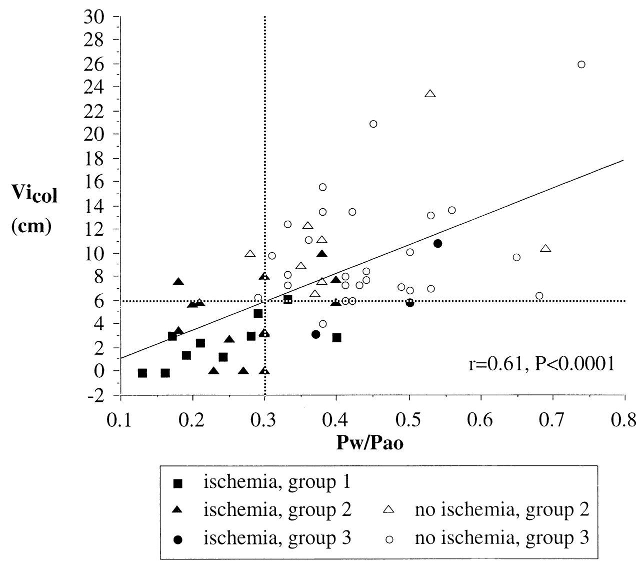

Figure 2. Relationship between the mean coronary wedge pressure/mean aortic pressure ratio (Pw/Pao) and the total collateral blood flow velocity integral (Vi_{col}) in patients split by the presence of ischemia and angiographical grading of collateral vessels (group 1–3).

Hemodynamic evaluation of the collateral vascular circulation. Logistic regression analysis revealed Pw/Pao and Vi_{col} as independent predictors of the protective effect of collateral vessels. Both hemodynamic variables are required to calculate the collateral vascular resistance and peripheral myocardial vascular resistance of the recipient coronary artery. Experimental work of Schaper et al. (24) using canine subjects showed the relevance of measuring both variables as a decrease in collateral resistance during chronic coronary occlusion of 18 weeks resulted in an increase in collateral blood flow while the coronary wedge pressure remained unchanged. This observation is explained by a concomitant decrease in both the collateral vascular resistance (resulting in an increase of collateral flow and Pw/Pao) and the peripheral vascular resistance of the recipient coronary artery (resulting in an increase in collateral flow and a decrease in Pw/Pao). These experimental findings were confirmed in a recent clinical study evaluating the pharmacological modulation of collateral vascular resistance by vasodilators (21). These studies emphasize the need for measuring both pressure and flow-derived variables of the collateral vascular circulation providing insight into the dynamics of the coronary collateral circulation in humans.

Study limitations. The accuracy of blood flow velocity analysis in the recipient coronary artery for the assessment of collateral flow has not been validated against a "gold standard" for myocardial perfusion in humans. Positron emission tomography has been applied to assess myocardial perfusion in collateral-dependent vascular areas in chronic coronary occlusion (25,26). However, this technique precludes the assessment of recruitable collateral flow.

This study was performed in a selected group of patients with one-vessel disease. The medical therapy of the patients studied was not uniform and this may have contributed to the variations observed among the patients. The angiographic grading of collateral vessels is sensitive to variations in the technique applied and is subject to intra- and interobserver variability. Moreover, intracoronary blood flow velocity assessment is a sensitive technique for the detection of alterations in blood flow, but this method for the assessment of collateral flow is prone to technical failures due to the position of the guide wire tip relative to the input of collateral flow and the induction of artifacts by contact with vessel wall and excessive guide wire motion within the target vessel.

Furthermore, the potential decrease of the caliber of the artery distal to the balloon during balloon occlusion may result in an overestimation of collateral blood flow in patients with low blood flow velocity signals and a low mean coronary wedge pressure. Therefore, it is possible that the differences observed in collateral blood flow velocity between patients with and without recruitable collateral vessels are an underestimation of the true differences in collateral volume flow due to this phenomenon.

The functional significance of collateral vessels during coronary occlusion was judged by electrocardiographic monitoring only during brief coronary occlusion and the method was not expanded to include hemodynamic monitoring or assessment of global or regional ejection fractions. The development of electrocardiographic signs of ischemia during coronary occlusion may be influenced by the relationship between the size of the myocardium "at risk" and extent of the collateral-dependent vascular bed which were not assessed in the present study. Finally, the limited number of studies performed regarding the coronary collateral circulation evaluated in an angioplasty model requires confirmation of these findings by other investigators.

Clinical implications. The present study documents the maximal collateral vascular circulation in obstructive coronary artery disease represented by a Pw/Pao of ~0.45 and a Vi_{col} of ~10 cm in patients with recruitable or spontaneously visible collateral vessels. Obviously, this extent of the collateral vascular circulation is inadequate for myocardial perfusion in order to relieve patients from stress-induced symptoms. Nevertheless, it is possible that symptomatic patients are a selection of patients with inadequate adaptation of the coronary collateral circulation as compared with asymptomatic patients with coronary artery disease. At present the factors determining the maximal collateral vascular circulation are the subject of experimental studies that may lead to new treatment modalities in the near future.

A limited number of studies concern the pharmacological responsiveness of collateral vessels showing an increase of flow to collateral-dependent myocardium by vasodilators such as nitroglycerin and adenosine (21,27,28). Preliminary data suggest that the pharmacological modulation of collateral resistance is more pronounced in patients with spontaneously visible collateral vessels as compared with patients with recruitable collateral vessels (21). This phenomenon may be related to the morphology of the collateral vascular wall as suggested by experimental studies (29). Recent clinical studies have indicated a response in the collateral vascular growth in patients with peripheral artery disease after treatment with growth factors or gene therapy (30,31). Nevertheless, our current understanding regarding the process of the collateral vascular circulation stimulation is incomplete and the subject of intensive experimental research. The present study emphasizes the relevance of using hemodynamic variables for evaluation of the collateral vascular circulation in humans.

However, the evaluation of new pharmacological agents or gene therapy requires quantitative assessment of the collateral vascular circulation providing insight into the modulation of collateral flow indexes using noninvasive techniques such as positron emission tomography or by using hemodynamic variables in invasive techniques as shown in the present study.

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